Cardiac Lesions in Rats Fed Rapeseed Oils

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ABSTRACT

Fully refined rapeseed oils containing different amounts of erucic acid (1.6%, 4.3% and 22.3%) were fed, at 20% by weight of diet, to weanling male and female Sprague-Dawley rats for periods up to 112 days. Transient myocardial lipidosis characterized by accumulation of fat droplets in myocardial fibers was marked in male and female rats fed oxidized and unoxidized rapeseed oil containing 22.3% erucic acid, moderate with rapeseed oil containing 4.3% erucic acid and very slight in rats fed rapeseed oil containing 1.6% erucic acid. Peak intensity of myocardial lipidosis occurred at three to seven days and regressed thereafter. Focal myocardial necrosis and fibrosis occurred in male rats fed rapeseed oils containing different levels of erucic acid for 112 days. The incidence of myocardial necrosis and fibrosis was markedly lower in female rats, and the incidence of these lesions in either sex was not affected by the state of oxidation of these oils. In a second experiment, male rats were fed diets containing crude, partially refined or fully refined rapeseed oils. There was no correlation between the number of foci of myocardial necrosis and fibrosis and the state of refinement of the oils, but there were generally fewer lesions in rats fed those oils having the lowest levels of erucic acid.

RÉSUMÉ

On a servi à des rats mâles et femelles récemment sevrés, de lignée Sprague-Dawley, des huiles de colza, à raison de 20% du poids de leur ration, durant des périodes échelonnées jusqu'à 112 jours. Ces huiles étaient complètement raffinées mais contenaient différentes quantités d'acide érucique (1.6%, 4.3% et 22.3%). On a observé une lipidose myocardiaque transitoire, caractérisée par l'accumulation de gouttelettes lipidiques dans les fibres musculaires cardiaques; ces lésions étaient prononcées chez les rats mâles et femelles nourris à l'huile de colza oxydée et non oxydée contenant 22.3% d'acide érucique, mais elles étaient modérées et bénignes lorsque ce taux était respectivement de 4.3% et 1.6%. La fréquence maximale d'apparition des lésions se situait entre le troisième et le septième jour pour disparaître ensuite progressivement. On observa des foyers de nécrose et de fibrose du myocarde, chez les rats mâles recevant durant 112 jours des huiles de colza contenant différents taux d'acide érucique. L'incidence de la nécrose et de la fibrose du myocarde était sensiblement plus basse chez les femelles; de plus, chez l'un et l'autre sexe elle n'était pas reliée à l'état d'oxydation des huiles. Dans une seconde expérience, on a servi à des rats mâles des rations contenant des huiles de colza brutes, partiellement raffinées et complètement raffinées. On ne nota aucune relation entre le nombre de foyers de nécrose et de fibrose du myocarde et le degré de raffinement des huiles, bien qu'en général, on constata moins de lésions chez les rats recevant des huiles possédant les taux les plus bas d'acide érucique.

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INTRODUCTION

Rapeseed oils, as ingredients of various salad oils, shortenings, and margarines are used fairly extensively in human diets. Rapeseed oils differ from most other edible oils in that they contain erucic acid (13-cis-docosenoic acid) and have low levels of saturated fatty acids (6). Oils extracted from different varieties of rapeseed may be characterized by the amount of erucic acid which they contain. The content of erucic acid may range from approximately 50% in oil extracted from some rapeseed varieties to less than 1% from some of the new low-erucic-acid varieties of rapeseed.

Various lesions in the heart and other organs have been described in experimental animals fed rapeseed oil containing a high level of erucic acid. These lesions include: cardiac lipidosis in rats (3, 4, 8, 11), gerbils (8), monkeys (9), pigs (9, 27), ducklings (2, 17), chickens and turkeys (17); lesions described as myocardial necrosis and/or myocarditis in rats (3, 4, 9, 19, 20, 21) and rabbits (25); hemolytic anemia and hydropericardium in guinea pigs (26); anemia, hydropericardium, ascites and hepatic fibrosis in chickens and ducks (2, 17), and anemia and myocardial granulomas in turkeys (17). There are no reports of any lesions in man being attributed to ingestion of these oils.

Cardiac lipidosis in rats is generally attributed to erucic acid since oils from recently developed varieties of rapeseed have low levels of erucic acid and produce very little or no fatty deposition in rat myocardium (1, 4). However, there is no general agreement on the incidence and severity of myocardial necrosis in rats fed rapeseed oils containing low levels of erucic acid. Some reports claim that myocardial necrosis is produced by oils with high or low levels of erucic acid (19, 20) while other reports claim that it is produced only by oils with high levels of erucic acid (3, 4).

This investigation was undertaken to study the incidence and types of cardiac lesions in rats fed various rapeseed oils and to determine the effect of oxidation and commercial processing procedures on the pathogenicity of these oils.

MATERIALS AND METHODS

Dietary Oils

Soybean oil, corn oil and the following rapeseed oils[1] were used (Table I): Oro rapeseed oil (RSO) from *Brassica napus* var. Oro containing 1.6% erucic acid; Span RSO from *B. campestris* var. Span containing 4.3% erucic acid; Regular RSO from a mixture of *B. campestris* var. Arlo (15%) and var. Echo (85%) containing 22.3% erucic acid. All oils had antioxidant (13.3% butylated hydroxy toluene, 3.3% propyl-gallate, 3.3% citric acid, 2.0% butylated hydroxyanisole and the remainder monoglyceride citrate and vegetable oil) added at

[1]Span RSO and Regular RSO were obtained from Western Canada Processors, Lethbridge, Alberta, and ORO RSO was obtained from Co-operative Vegetable Oil Ltd., Altona, Manitoba. Corn oil was obtained from St. Lawrence Starch Co. Ltd., Port Credit, Ontario. Soybean oil was obtained from Canada Packers Ltd., Toronto, Ontario.

TABLE I. Cardiac Lesions in Rats fed Rapeseed Oils — Experiment I. Diets

Diet (Basal + Oil)	Lipid in Diet (Wt %)	Erucic acid (Mole %)	Number of Rats fed Diets			
			Unoxidized Oils		Oxidized Oils	
			Female	Male	Female	Male
Corn	20	0	84	42	42	42
Soy	20	0	84			
Oro RSO[a]	20	1.6	84	42	42	42
Span RSO	20	4.3	84	42	42	42
Regular RSO	20	22.3	84	42	42	42
Lard	5	0	84	42		
Purina Chow	1.9	0	84			

[a]RSO = rapeseed oil

TABLE II. Cardiac Lesions in Rats fed Rapeseed Oils — Experiment I. Accumulation of Lipid in Myocardium of Female Rats Fed Unoxidized Oils

Diet (Basal + Oil)	Lipid in Diet (Wt %)	Erucic Acid (Mole %)	Days on Diet					
			3	7	14	28	56	112
Oro RSO[a]	20	1.6	+[b]	±	±	±	−	−
Span RSO	20	4.3	++	++[c]	+	+	−	−
Regular RSO	20	22.3	+++[c]	+++[c]	+++[c]	++	±	±
Corn	20	0	—	—	—	—	—	—
Soy	20	0	—	—	—	—	—	—
Lard	5	0	—	—	—	—	—	—
Purina Chow	1.9	0	—	—	—	—	—	—

[a]RSO = Rapeseed Oil
[b]Results represent degree of lipid accumulation as determined by oil-red-O stained sections — no fat present, ± very slight, + slight, ++ moderate, +++ marked
[c]Diffuse vacuolation of myocardial fibers was present in sections stained with hematoxylin and eosin

the rate of 750 g per metric ton. The peroxide value of the oils was in the range of 3-6 mEq per kg oil.

Oxidized Oils

The oxidized oils used in the study (Tables I and III), were prepared from the above oils in the laboratory by continuously and vigorously bubbling air through the oils at 60°C for 15 days. At the end of the oxidation the peroxide values, determined according to Official Methods of Analysis (16) were corn oil, 27.7; Oro RSO, 35.1; Span RSO, 25.5; Regular RSO, 22.2 mEq per kg oil.

Oils at Various Stages of Refining

Samples of oils were removed at various stages of refining of the rapeseed oils at the commercial processing plant and were used for the experiment described under Table IV. The various stages in the processing consist of (i) expeller or solvent extraction to get the crude oil from the seeds, (ii) degumming by the addition of 1.5% water to the oil, and removing the precipitated gums by centrifugation, (iii) alkali refining to remove the free fatty acids and subsequent washing of the oils with water to remove the alkali, (iv) bleaching by the addition of clay and (v) deodorizing by passing steam through the oil under reduced pressure. In some instances, the oils were further refined by "winterizing", a process in which the oil is cooled to precipitate the waxes, which are removed by centrifugation.

Animals and Diets

Male and female Sprague-Dawley rats (40 to 60 g) were purchased from Bio-Breeding Laboratories. Ottawa, and kept in pairs of the same sex in galvanized cages. One diet was a laboratory stock diet[2]. The other diets were semi-synthetic containing (by weight) 20% vitamin free casein, 20% sucrose, 30% corn starch, 1% vitamin mixture, 4% salt mixture, 5% pure wood cellulose and 20% test oils. In one semi-synthetic diet, 20% oil was replaced with 5% lard and 15% corn starch. The vitamin and salt mixtures provided these nutrients as per NCR requirements and the composition of these mixtures is fully described elsewhere (14).

Two experiments were conducted. Experiment I is summarized in Table I. In this experiment six groups of 84 females and five groups of 42 male rats were fed basal diets with added unoxidized oils and four groups of 42 female and four groups of 42 male rats were fed basal diets with added oxidized oils. One group of 84 female rats was fed Purina Laboratory Chow.[2] The oils included: 1) Oro RSO, 2) Span RSO, 3) Regular RSO, 4) Corn oil, 5) Soy bean oil and 6) lard. Fourteen female rats from each group fed unoxidized oils and the group fed Purina Chow were killed on days 3, 7, 14, 28, 56 and 112. Fourteen rats from all the remaining groups were killed on days 7, 28 and 112. Four rats were used for biochemical studies (14) and ten rats were used for histopathology.

[2]Purina Chow from Ralston-Purina Co., St. Louis, Missouri.

TABLE III. Cardiac Lesions in Rats fed Rapeseed Oils — Experiment I. Myocardial Necrosis and Fibrosis

Diet (Basal + Oil)	Lipid in Diet (Wt %)	Unoxidized Oils Females Days on Diet 7	28	112	Males 7	28	112	Oxidized Oils Females Days on Diet 7	28	112	Males 7	28	112
Oro RSO[a]	20	0[b]	1	2	0	2	7	1	4	1	0	1	8
Span RSO	20	0	1	0	0	1	7	0	1	3	0	2	7
Regular RSO	20	0	2	0	0	2	7	0	0	1	0	0	8
Corn	20	0	0	1	0	0	4	1	0	1	0	0	0
Soy	20	0	1	2	NF[c]	NF	NF	NF	NF	NF	NF	NF	NF
Lard	5	0	0	0	0	0	1	NF	NF	NF	NF	NF	NF
Purina Chow	1.9	1	1	2	NF	NF	NF	NF	NF	NF	NF	NF	NF

[a]RSO = Rapeseed Oil
[b]Numbers indicate the number of hearts from ten rats with necrotic, fibrotic or infiltrative lesions
[c]NF = Diet not fed

TABLE IV. Cardiac Lesions in Rats fed Rapeseed Oils — Experiment II. Effect of Feeding Various Oils at Different Stages of Commercial Refining

Diet (Basal + Oil)	Lipid in Diet (Wt %)	Erucic Acid (Mole %)	No. of Lesions[a]	No. of Rats Affected	No. of Lesions Per Rat (mean of 10 rats)
Crude Oro RSO	20	0.9	25	8	2.5
Degummed Oro RSO	20	2.5	53	10	5.3
Degummed alkali refined Oro RSO	20	1.8	18	8	1.8
Degummed, alkali refined, bleached deodorized Oro RSO	20	1.8	7	4	0.7
Degummed alkali refined, bleached, deodorized, winterized Oro RSO	20	1.4	72	10	7.2
Crude Span RSO	20	4.7	150	9	15.0
Degummed, alkali refined, Span RSO	20	5.0	69	8	6.9
Degummed, alkali refined, bleached, deodorized Span RSO	20	5.1	146	10	14.6
Crude Regular RSO	20	25.7	99	10	9.9
Degummed, alkali refined Regular RSO	20	25.4	194	10	19.4
Degummed, alkali refined, bleached, deodorized Regular RSO	20	25.8	167	10	16.7

[a]Number indicates the number of necrotic or fibrotic lesions found in ten hearts (three sections from each heart)

The rats were killed by exsanguination while under ether anesthesia. Pieces of all tissues were fixed in 10% neutral buffered formalin. Following fixation, portions of all hearts and other selected tissues were dehydrated, embedded in paraffin, sectioned at 6 μ and stained with hematoxylin and eosin. A central section from the apex to the base including the interventricular septum and the atrial and ventricular walls was taken from each heart. Frozen sections from the hearts of all female rats (Table II) and from at least 30% of all male rats killed on days 7, 28 and 112 were stained with Oil red O.

In experiment II, 13 groups of ten male rats were fed basal diets with added crude unoxidized rapeseed oils or oils subjected to various processes used in the extraction and storage of rapeseed oils (Table IV). All rats from each group were killed and necropsied at 112 days. The necropsy and histological procedures were the same as in experiment I except two additional sections

of each heart were made parallel to and equidistant from the central section in the middle of each half of the heart. Oil red O stains were not used.

RESULTS

In female rats fed unoxidized Regular, Span or Oro RSO, droplets of lipid were detected as red globules in sections of myocardium stained with Oil red O. No globules were detected in rats fed Purina Laboratory Chow (Fig. 1). The fat globules in rats fed rapeseed oils were more numerous in the ventricular walls and interventricular septa than in the atria. The globules were 1-8 μ in diameter in linear arrays within the muscle fibers (Figs. 2-4). Although widely disseminated, there were more globules in some foci than in others (Fig. 4). Rats fed Regular RSO and killed on days 3, 7 and 14 or rats fed Span RSO and killed on day 7 had vacuoles in the myocardial fibers in sections stained with hematoxylin and eosin (Fig. 5).

The degree of lipid accumulation varied according to the type of rapeseed oil and the duration of feeding. On days 3 and 7 the accumulation was very marked in rats fed Regular RSO, moderate in rats fed Span RSO and very slight in rats fed Oro RSO (Table II and Figs. 2-4). The amount of lipid decreased after day 7, and after day 28 no lipid was detected in the myocardium of rats fed Span or Oro RSO. Rats fed Regular RSO retained the globules of lipid longest and a few globules were present at day 112. Examination of hearts from randomly selected male rats fed oxidized and unoxidized oils and female rats fed unoxidized oils revealed lipid accumulation similar to that in female rats fed unoxidized oils. Slight accumulation of lipid also occurred in the skeletal muscles (diaphragm, masseter and semimembranosus) in the same pattern as in the hearts of rats fed Regular, Span or Oro RSO.

A few scattered focal interstitial accumulations of mononuclear cells were seen in hearts of male and female rats of all ages. These scattered lesions were detected in only a few rats from all groups fed the vegetable oils as well as rats fed Purina Chow.

Male rats fed Regular, Span or Oro RSO and killed on day 112 had distinct foci of

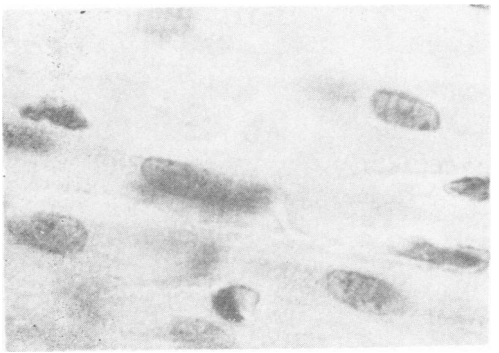

Fig. 1. Myocardium of female rat fed Purina chow and killed on day 3. No fat droplets in myocardial fibers. Oil red O. X600.

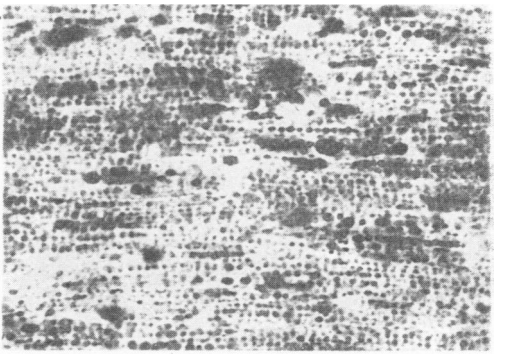

Fig. 2. Myocardium of female rat fed Regular RSO and killed on day 7. Note massive accumulation of fat droplets in myocardial fibers. Oil red O. X600.

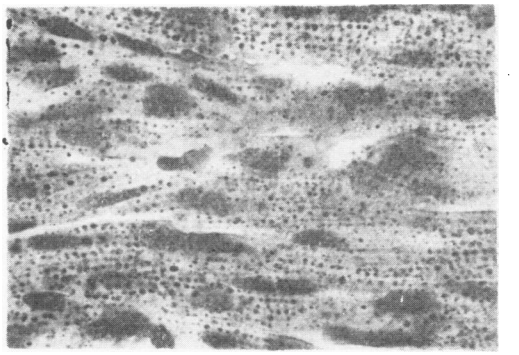

Fig. 3. Myocardium of female rat fed Span RSO and killed on day 7. Moderate accumulation of fat droplets. Oil red O. X600.

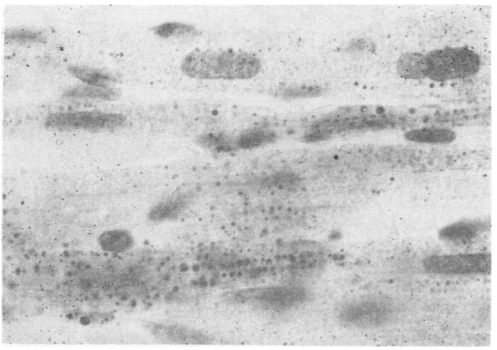

Fig. 4. Myocardium of female rat fed Oro RSO and killed on day 3. Very slight accumulation of fat droplets. Oil red O. X600.

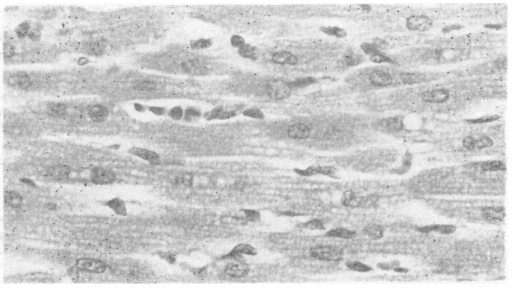

Fig. 5. Myocardium of female rat fed Regular RSO and killed on day 7. Vacuoles in myocardial fibers. H & E. X600.

necrosis and fibrosis in myocardium (Table III). These lesions were rarely observed in the hearts of female rats (Table III). The incidence of myocardial necrosis and fibrosis was not affected by feeding of oxidized oil.

In experiment II, foci of necrosis and fibrosis occurred in rats of all groups. There was no consistent correlation between the stage of refinement and the number of lesions in myocardium. Generally, rats fed Oro RSO had fewer lesions than rats fed the other oils. (Table IV).

The areas of necrosis and fibrosis varied from small foci 10 μ in diameter involving one fiber, to large oval or irregularly shaped regions approximately 2 mm in diameter. They were randomly distributed in the ventricular walls and interventricular septum. No areas of necrosis or fibrosis were detected in the atrial walls.

Acute and chronic lesions frequently were present in the same heart. Acute lesions consisted of small or large foci in which the myocardial fibers were hyalinized, swollen, fragmented, and the muscle nuclei were pyknotic (Figs. 6 and 7). There was hemorrhage in addition to myocardial necrosis in some foci (Fig. 8). Early acute lesions contained only a few macrophages (Fig. 6), but in more advanced lesions. there were many closely packed macrophages, and a few fibroblasts (Fig. 9). In a few chronic lesions, there were scattered hyalinized muscle fibers. Chronic lesions were round or linear areas of fibrous connective tissue (Fig. 10), some of which contained macrophages with brown intracytoplasmic granules. These granules were stained blue by the Prussian blue technique indicating the presence of hemosiderin.

Although lesions occurred in four male rats fed corn oil for 112 days, only two of these hearts had lesions of overt necrosis similar to those in rats fed rapeseed oils.

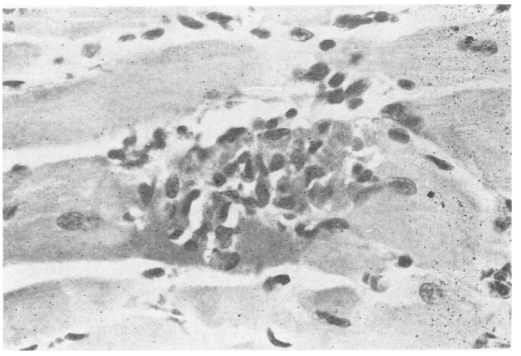

Fig. 6. Myocardium of male rat fed Regular RSO and killed on day 112. Small focus of necrosis and a few macrophages. H & E. X600.

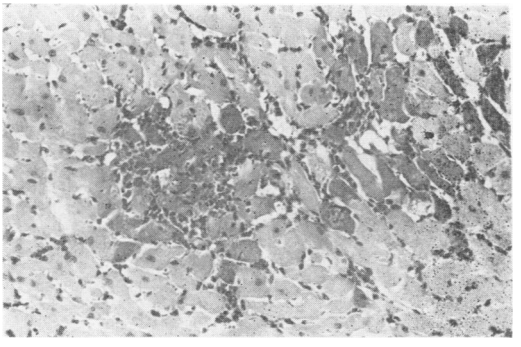

Fig. 7. Myocardium of male rat fed Regular RSO and killed on day 112. Foci of necrosis. Note hyalinized fibers with pyknotic nuclei and accumulation of a few phagocytes. H & E. X216.

DISCUSSION

The results of this study indicate that feeding Regular, Span or Oro rapeseed oils at the levels used in this experiment caused transient cardiac lipidosis in male and female rats. It was clearly demonstrated that the accumulation of lipid was marked in rats fed Regular RSO, moderate in rats fed Span RSO, and very slight in rats fed Oro RSO. Lipid persisted longest in rats fed Regular RSO. The fairly close correlation between the gradation of cardiac lipidosis caused by Regular, Span and Oro RSO, and the amounts of erucic and eicosenoic acids which these oils contain (14) suggests that one or both of these fatty acids play an important role in the accumulation of cardiac lipid. Previous studies indicate that rats fed synthesized oils with high content of eicosenoic acid developed less severe cardiac lipidosis than rats fed oil with high erucate content (10).

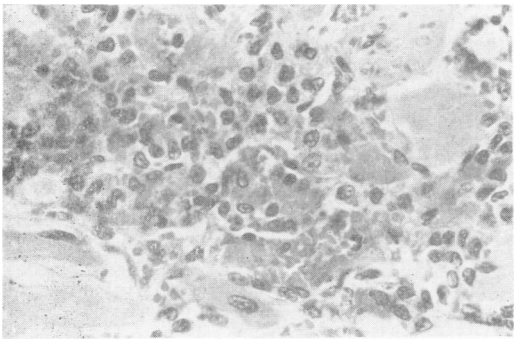

Fig. 8. Myocardium of male rat fed Regular RSO and killed on day 112. Focal necrosis and hemorrhage. H & E. X600.

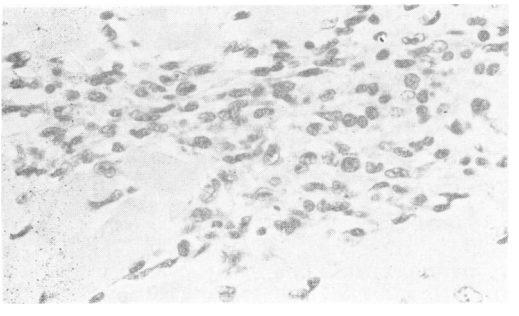

Fig. 9. Myocardium of male rat fed Oro RSO and killed on day 112. Irregular shaped area of replacement of myocardium with macrophages and fibroblasts. H & E. X600.

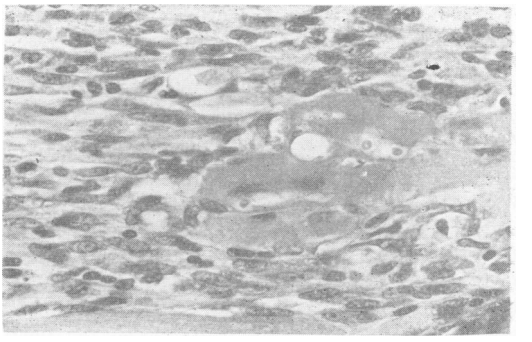

Fig. 10. Myocardium of male rat fed Regular RSO and killed on day 112. Part of scar of fibrous connective tissue containing an island of myocardial fibers. H & E. X600.

Oil red O is absorbed mainly by unsaturated triglycerides, cholesterol esters and free fatty acids (5). Thus the accumulation of more fat or the accumulation of fat with a low ratio of saturated to unsaturated fatty acids would result in an increased amount of Oil red O positive material. Biochemical studies indicated that on day 7 of the experiment, there was an increase in total cardiac lipids in rats fed Regular RSO but not in those fed Span or Oro RSO (14). In all three groups, the ratios of saturated to unsaturated fatty acids in the heart were lower than in rats fed corn oil or lard. The accumulation of cardiac neutral lipids with a high degree of unsaturation in rats fed rapeseed oils would account for the amount of Oil red O positive material present.

The results of biochemical studies suggest that the myocardial fat droplets in rats fed rapeseed oils contain a significant amount of erucic acid especially in rats fed Regular RSO (11, 14). This fatty acid is present mainly in the triglyceride fraction (8). Inefficient activation of erucic acid to erucyl CoA and a low level of activity of triglyceride lipase and enzymes of beta-oxidation for erucic acid probably contribute to the accumulation and retention of cardiac lipid (14).

Foci of myocardial necrosis and fibrosis occurred in male rats fed Regular, Span or Oro RSO for 112 days. Some previous reports indicated that rapeseed oils with either high or low levels of erucic acid cause myocardial necrosis (19, 20). Other reports suggest that only rapeseed oils with high levels of erucic acid cause myocardial necrosis (3, 4). Our results confirm the reports suggesting that prolonged feeding of male rats with oils either high or low in

erucic acid is associated with focal myocardial necrosis and fibrosis. In experiment II, lesions occurred in all groups of rats. Although there was marked variation among groups, the generally fewer numbers of lesions in rats fed Oro RSO suggests that this oil is less cardiopathogenic than Regular or Span RSO.

In several lesions, the presence of pyknotic myocardial nuclei as well as severe fragmentation and hyalinization of the fibers indicate that overt myocardial necrosis had occurred. The occurrence of both acute and chronic lesions in male rat hearts examined at day 112 suggests that the focal necrosis did not occur at one time but was continuous or recurrent during at least part of the experiment. There was no clear association between cardiac lipidosis and necrosis. The initial lesion of focal necrosis appeared to be followed by accumulation of macrophages removing the remnants of degenerate fibers. Replacement of the macrophages with fibrous connective tissue resulted in fibrotic scars.

The mechanisms involved in the development of myocardial necrosis in male rats fed rapeseed oils were not determined. Although necrosis occurred subsequent to cardiac lipidosis, the regression of most of the cardiac lipid before the onset of necrosis, the very mild accumulation of lipid in rats fed Oro RSO, and the predominance of necrosis in male rats suggest that features other than or in addition to the accumulation of lipid in myocardium are necessary for the development of myocardial necrosis. Previous studies indicate that when the feeding of rapeseed oil to growing rats is discontinued at the point of peak lipid accumulation no myocardial fibrosis develops (6).

Kaunitz and Johnson (13) reported that myocardial necrosis in rodents could be caused by feeding mildly oxidized fats and oils. In the present study, oxidation of the oils used did not increase the incidence of myocardial necrosis in rats. The results from using oils in different stages of refinement suggest that commercial processing does not alter the effect of rapeseed oils on rat myocardium.

Any explanation of the pathogenesis of myocardial necrosis must take into account the predominance of lesions in male rats and the occurrence of necrosis with diets either high or low in erucic acid. Myocardial necrosis in rodents has been associated with various experimental conditions (18) including high fat-low protein diets (28), high triglyceride diets (29), thiamine deficient diets (7), choline deficient diets (24, 27), potassium deficient diets (12, 23) and administration of hormones (15, 22). It has been demonstrated that the degree of myocardial necrosis induced in mice with hydrocortisone is influenced by sex (15) and that oral administration of plant or animal fats increases the degree of myocardial necrosis produced in rats by methyl-9 chlorocortisol and disodium phosphate (22). It is evident that several nutritional deficiencies and imbalances may cause myocardial necrosis in rodents. The role of sex and hormones (if any) in the development of myocardial necrosis in rats fed rapeseed oils are of particular interest in the current study. These features are now under investigation.

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BOOK REVIEW

LYMPHOCYTIC CHORIOMENINGITIS VIRUS AND OTHER ARENAVIRUSES. *Edited by F. Lehmann-Grube. Published by Springer-Verlag, Berlin, Heidelberg and New York, 1973. 339 pages. Price $18.10.*

This publication is a collection of 28 papers presented at a Symposium held at the Heinrich-Pette-Institut für experimentelle Virologie und Immunologie, Universität Hamburg in October 1972. Previous symposia in this series were on demyelinating encephalitis in 1962, and on the pathogenesis and etiology of demyelinating diseases in 1967.

Lymphocytic choriomeningitis (LCM) was discovered over 40 years ago, and research on the disease and its causative virus, now the type species of the Arenavirus group, has had an interesting history. For a long period, LCM research was pursued at a relatively low level, involving a few widely scattered investigators. More recently, however, LCM gained popularity as a research model for the investigation of some basic immunological problems, following Burnet and Fenner's concept of self-recognition, itself based partly on observations made on mice persistently infected with LCM virus. Further interest was generated by Hotchin's idea that experimental LCM in adult mice represented a viral-induced immune disease. Today, there is great interest in the interactions between LCM virus and the mouse in the study of immunological tolerance, immunopathology, latent viral infection and the so-called slow virus diseases, as evidenced by the presence of almost 50 participants at this highly specialized Symposium.

Following a general introduction on LCM virus research by Traub, one of the very early pioneers in this field, the scientific papers included in this volume are divided into six sections, four of which deal exclusively with LCM. The first of these four sections relates to the purification and chemical, physical and antigenic properties of LCM virus, and this is followed by a series of three papers on the interactions of the virus with cells. The third section, which contains seven papers, is devoted to a detailed consideration of LCM as a persistent infection, and includes a discussion by Hotchin of the phenomenon of cyclical transient infection in relation to persistent infection of the mouse with LCM virus. The final group of LCM papers cover the acute and chronic disease in man and animals, including pathogenesis, immunology, epidemiology and a description of the morphological changes in the brain. The final sessions of the Symposium were devoted to a relatively superficial consideration of arenaviruses other than LCM, an area, in which there is clearly less interest and research activity. Six papers deal with viruses of the Hemorrhagic Fever group, and the final paper is by Casals and Buckley, on Lassa Fever virus.

The book is obviously an important contribution to the literature on LCM, persistent infections and virus-induced immune disease. It will be convenient to those working in these fields to find so many papers describing recent research findings incorporated in a single volume, rather than distributed among a variety of primary journals. — *J. B. Derbyshire.*